

- Walking Impairment Questionnaire (WIQ).

- patient's quality of life assessment via the Medical Outcomes Scale Short Form 36 (SF-36).

Blood samples were obtained prior to treatment, and at post-randomization weeks 4, 12, and 24. Safety endpoints included: 12-lead EKG (obtained pre-treatment, and at post-randomization weeks 4, 12, and 24). AE and vital signs were assessed pre treatment, and at post-randomization weeks 2, 4, 8, 12, 16, 20, and 24). Serum chemistry and hematology were obtained pre-treatment, and at post-randomization weeks 4, 12, and 24. Urinalysis was obtained pre-treatment, and at post-randomization week 24.

8.2.5.2 @Measurement methods (study 21-96-202)

The "delayed-incline" treadmill method was used wherein incline loading was delayed until the 3rd minute of walking, and then gradually increased by 3.5% increments every 3 minutes (with speed constant at 3.2 km/h (2 mph). Walking tests were only to be stopped for claudication of sufficient severity to cause the subject to be unable to continue walking. There was no prespecified provision for tests to stop for such reasons as reaching an arbitrarily long duration or distance of walking.

Quality of life assessment via the Medical Outcomes Scale Short Form 36 involved the following subscales: Bodily Pain (2 items), General Health Perception (5 items), Mental Health (5 items), Physical Function (10 items), Role Limitations Due to Emotional Problems (3 items), Role Limitations Due to Physical Health (4 items), Social Function (2 items), Vitality (4 items), and Reported Health Transition (1 item). For all subscales, higher scores indicated better functioning.

8.2.6 @Statistical analyses. (study 21-96-202)

ANOVA and repeated measures ANOVA were pre-specified to be used to analyze ACD and ICD, in a model including treatment and center as factors.

The primary analysis was ANOVA, while repeated measures ANOVA was done as a secondary analysis. Physician and patient assessments of subjective improvement were to be analyzed using ordinal logistic regression.

Secondary comparisons were to be CLZ vs placebo, and PTX vs placebo (with the prespecified primary analysis a comparison between CLZ and PTX).

Analyses were to be based on two-sided testing at an alpha level of 0.05.

The sample size was calculated on the basis of the primary endpoint, making the following assumptions:

- $\log(\text{ACD at week 24/pre-treatment ACD})$ would equal 0.41 for CLZ and 0.14 for placebo.

- detection of 60% improvement above placebo response.
- power of 95%
- two-sided alpha level of 0.05.

An interim analysis was initially specified in protocol amendment 4, but was later deleted (in protocol amendment 5) reportedly because the trial was progressing to rapid completion.

8.2.7 @Results other than efficacy outcomes (study 21-96-202):

8.2.7.1 @Covariates:

Demographic and pre-treatment characteristics are shown in the table below. These covariates were well balanced.

Table: 6

**@Demographic and pre-treatment characteristics of subjects
in study 21-96-202:
(all-randomized¹³ dataset)**

	<i>CLZ</i> <i>100 mg</i> <i>bid</i>	<i>PTX</i> <i>400 mg tid</i>	<i>Placebo</i>
	<i>n= 227</i>	<i>n= 232</i>	<i>n= 239</i>
male	76%	78%	74%
age (mean)	66	66	66
Caucasian	89%	89%	89%
Black	8%	9%	8%
wt mean (kg)	81	82	81
concomitant tobacco use	41%	33%	38%
diabetes	32%	28%	31%
resting ABI			
mean	0.66	0.66	0.68
SD	0.18	0.21	0.42

[source: table 3, vol 3, submission 5/6/98; submissions 6/9/98 & 7/6/98]

8.2.7.2 @Disposition of subjects: (study 21-96-202)

The subject disposition is show below. In summary,

- 699 subjects were randomized (evenly distributing among treatment groups as 228 to CLZ, 232 to PTX, and 239 to placebo).
- one CLZ-randomized subject (#3773) was excluded by the sponsor

¹³ with the exception of one CLZ-randomized patient who was excluded by the sponsor.
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after reportedly withdrawing after randomization to cilostazol, but prior to either taking any drug or providing any post-baseline measurements.

543 subjects (distributed as: 205 CLZ, 212 PTX, 226 placebo) comprised the "efficacy" dataset. These received at least one dose of study medication, had at least one nonmissing pre-treatment walking test datum, and at least one nonmissing post-randomization walking test datum at any timepoint in the study. No subjects were reported as having missing pre-treatment walking test data.

The rate of total dropouts was comparable in the CLZ- and PTX-treated groups, and comparably higher than in the placebo group. The attributed reasons for dropouts are shown in the following table.

Table: 7
@Dropouts in study 21-96-202 (all-randomized¹⁴ dataset)

	<i>CLZ 100 mg bid</i>	<i>PTX 400 mg tid</i>	<i>Placebo</i>
	n = 227	n = 232	n = 239
<i>Dropouts for any AE</i>	38 (16.7%)	45 (19.4%)	23 (9.6%)
Total dropouts	61 (26.8%)	60 (25.9%)	38 (15.9%)
All dropouts, by reason:			
nonfatal AE	36	43	22
death	2 (0.88%)	2 (0.86%)	1 (0.41%)
general inability to continue ¹⁵	4	5	7
refusal to continue	5	4	3
inefficacy	3	2	1
started disallowed medication	3	2	1
lost to follow-up	3	1	1
revascularization	2	0	0
safety reasons ¹⁶	3	1	2

[source: table 2, vol 3, addendum 5/6/98; pg 103, addendum 7/6/98-A]

8.2.8 @Efficacy outcomes: (study 21-96-202)

¹⁴ except for one CLZ-randomized subject who was excluded by the sponsor.

for such reasons as family emergency, moving out of state, etc.

the CLZ dropouts for what was termed "safety reasons" were Patient #3625, Center 006; Patient 5136, Center 111; and Patient 6230, Center 110. More specific reasons for withdrawal were reportedly not captured, but the sponsor is attempting to obtain more information.

8.2.8.1 @Tests stopped for nonspecific reasons (study 21-96-202)

The stopping of final tests for nonspecific reasons (defined as reasons other than claudication) occurred in approximately 25% of CLZ-randomized subjects, 15% of placebo-randomized subjects, and 22% of OXP-randomized subjects. The nonspecific reasons included hypertension, arrhythmia, back pain, feet hurting, calf tightness, chest pain, dyspnea, and several others.¹⁷

8.2.8.2 @Primary efficacy analyses: (study 21-96-202)

At pre-treatment baseline, in the efficacy dataset, the raw mean trough ACD and trough ICD were comparable among the 3 treatment groups. These data are shown in the table below.

¹⁷ as per addenda submissions dated 5/15/98, and 6/9/98.

Table: 8

Baseline raw mean trough walking distances (in meters)
in study 21-96-202:

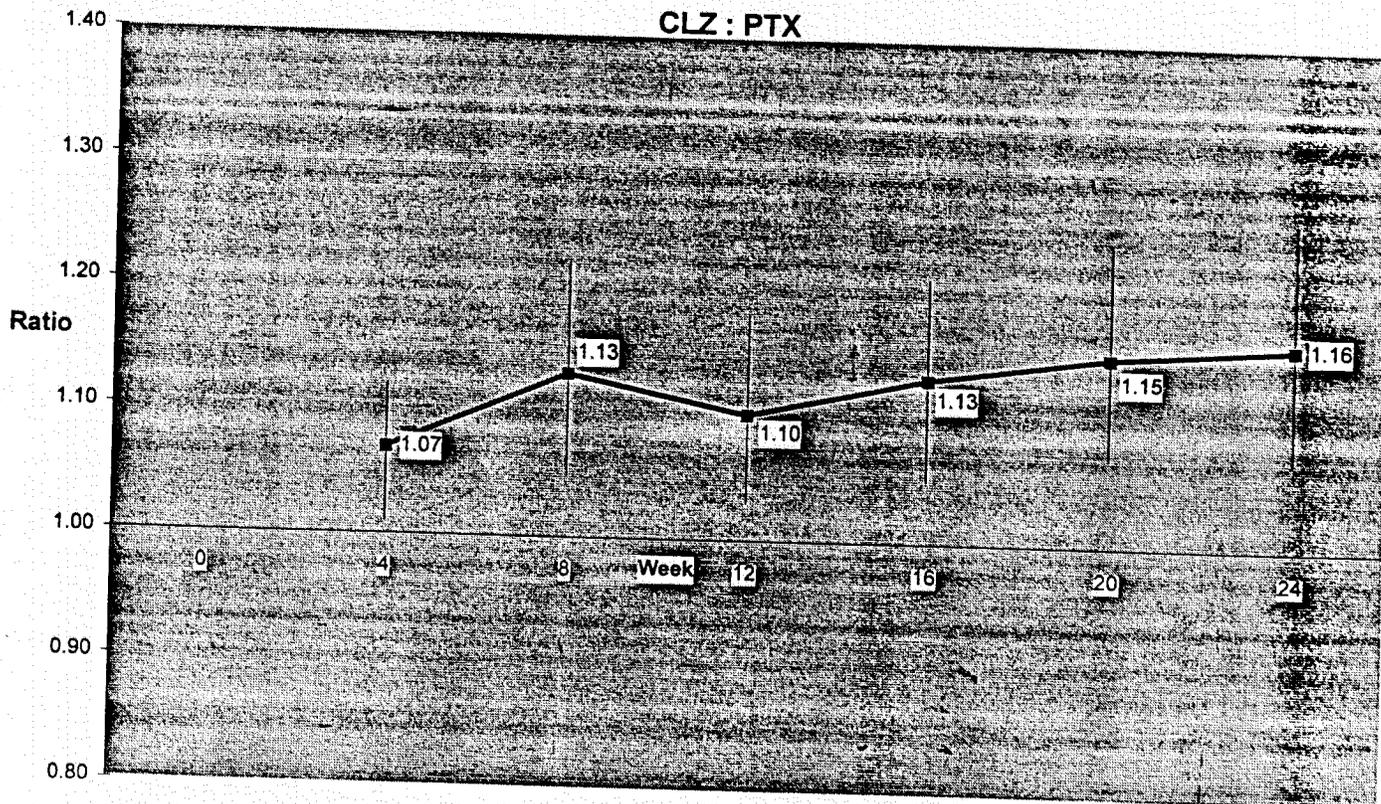
<i>baseline metric</i>	<i>CLZ 100 mg bid</i>	<i>PTX 400 mg tid</i>	<i>Placebo</i>
ICD	123.5	125.7	122.0
ACD	240.5	237.6	234.0

[source: table 4, vol 3, addendum 5/6/98]

The sponsor's results of the primary analysis (log transform, week 24, ITT/LOCF) showed the CLZ group to have a statistically distinguishable relative change from pre-treatment ACD at trough (CLZ : PTX ratio of 1.16, 95% CI = 1.07-1.26; p=0.0002). See the table below.

Figure: 4

Ratio (point estimate and 95% CI) of log transformed change from pre-treatment ACD, at trough (study 21-96-202, ITT/LCOF)



The comparison of CLZ to placebo yielded similar results, since PTX and placebo showed comparable treatment effects.

8.2.8.3 @Other efficacy analyses: (study 21-96-202)

There reportedly was neither a significant treatment-by-baseline interaction,¹⁸ nor a significant treatment-by-center interaction for ACD.

At week 24 the mean ratio (CLZ:PTX) of the change from pre-treatment ACD at trough was 1.13, and the mean ratio (CLZ:placebo) was 1.23.

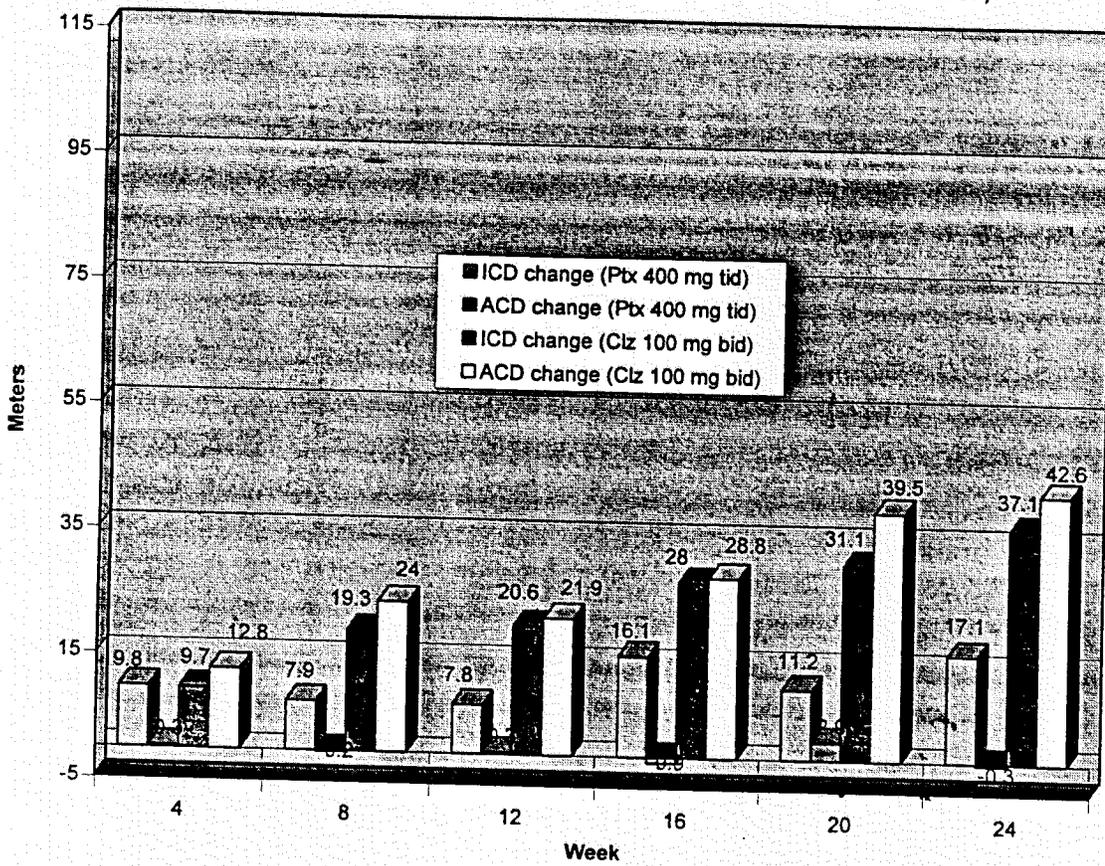
At week 24 in the "observed cases" dataset (in which no carry-forward was undertaken) the mean ratio (CLZ:PTX) of the change from pre-treatment ACD at trough was 1.16 (95% CI = 1.05-1.27). This result was consistent with the finding in the prespecified LOCF dataset. No "completers" dataset was captured.

The raw trough walking distances are shown in the figure below. This post-hoc examination of the data is presented for descriptive purposes. At trough, during week 24, the reported placebo-corrected mean changes from pretreatment ICD were 37.1 and 17.1 meters for the CLZ 100 mg bid vs PTX 400 mg tid groups, respectively. At this same time the change from raw mean pretreatment ACD was 107.3, 64.4, and 64.7 m in the CLZ 100 mg bid, PTX, and placebo groups, respectively (placebo-corrected changes being 42.6 and -0.3 meters for CLZ and PTX, respectively). See the figure below.

¹⁸ The study report incorrectly indicated that there was such an interaction.
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Figure: 5

Placebo-corrected change from raw mean pre-treatment
trough walking distance (study 21-96-202, ITT/LCOF)



The results of physician and patient subjective assessment of improvement, relative to pre-treatment, were as follows: according to physicians' opinions, 51% of CLZ subjects improved and 3% worsened, 38% of PTX subjects improved and 2% worsened, and 37% of placebo subjects improved and 6% worsened. According to patients' opinions: 51% of CLZ subjects improved and 6% worsened, 39% of PTX subjects improved and 6% worsened, and 34% of placebo subjects improved and 11% worsened.

Quality-of-life measurements reportedly showed the following (these should be considered no more than descriptive analyses, given the appreciable multiplicity problem): The Physical Health Concepts metric revealed a nonsignificant trend toward greater improvement for CLZ patients over OXP and placebo patients at week 24. The Physical Function metric at week 24 showed a mean change from baseline of 0.8, 3.0 and 1.8 for the placebo, CLZ, and OXP groups, respectively. The Bodily Pain metric (of physical well-being and disability as perceived by patients) at week 24 showed a mean change from baseline of 1.0, 5.2, and 1.6 for the placebo, CLZ, and OXP groups, respectively. With the Role-Physical metric at week 24, only patients in the CLZ group demonstrated improvement from baseline (with a mean change of 3.7). The Physical Component metric at week 24 showed a mean change from baseline of 1.7 for CLZ patients compared to 0.2 and 0.5 for patients in the OXP and placebo groups, respectively. The Mental Health Concepts metric (of both mental function and mental well-being), Role-Emotional metric, and Social Function metric showed no differences between the three treatment groups at week 24. The Mental Component metric at week 24 showed a mean change from baseline of -0.8 for CLZ patients compared to -0.6 and -1.3 for patients in the OXP and placebo groups, respectively. There were no differences between treatment groups in the General Health Perception score.

8.2.9 @Commentary on the evidence (study 21-96-202):

the primary (log-transformed) analysis showed the CLZ 100 mg bid group at trough on week 4 to have a small, statistically distinguishable change from pre-treatment ACD, relative to PTX. The point-estimated ratio of relative effect size (CLZ : PTX) was 1.16, with a 95% CI of 1.07-1.26, and a p value of 0.0002.

b. at trough on week 24, the placebo-corrected raw *mean* changes from pretreatment ACD were about 43 meters in the CLZ 100 mg bid group, and -0.3 meters in the PTX group, while the raw *median* changes were 24 m vs -8 meters, respectively.

c. there is no information as to whether CLZ was statistically distinguishable from PTZ at other times during the dosing interval (such as at peak).

d. by excluding subjects who used pentoxifylline within 30 days this plausibly enriched the sample with pentoxifylline non-responders and/or non-toleraters. To the extent that it was non-responders who enriched the sample, this would bias analyses towards underestimation of the general population responsiveness to PTX.

8.3 Study 21-94-201: !

3.1 @Design Summary (study 21-94-201)

This concurrent placebo-controlled, double-blind, parallel-group study randomized (in a 1:1 ratio) 394 subjects (peripheral atherosclerosis patients with moderately severe, stable, intermittent claudication) to receive placebo, or cilostazol given as a fixed 100 vs 200 mg/d dose in equally-divided twice-daily (50 or 100 mg bid) oral administrations for 24 weeks. The objectives were to assess safety (by observing, e.g., cardiovascular morbidity and all-cause mortality), and improvement in ACD, at trough, after 24 total months of therapy.

The chronology of this study's execution was reportedly as follows:

Table: 9

@Chronology of study 21-94-201

Event Completed	Date of Completion
Original Protocol	3/23/95
First Amendment	6/23/95
1st subject randomized	7/5/95
Last Subjects Final Follow-up	8/14/96
Final Analysis	8/12/97

[source: addenda dated 10/22/97 & 4/13/98]

8.3.2 @Enrollment criteria. (study 21-94-201)

Adult subjects (at least 40 years old) of both sexes were eligible for enrollment if they had atherosclerosis obliterans-induced¹⁹ intermittent claudication which was chronic, stable, and not associated with lower extremity ischemic rest pain, ischemic ulceration, gangrene, or Buerger's disease²⁰. To qualify for randomization, enrolled subjects had to meet additional qualifying criteria related to symptom severity, and symptom invariability (see below discussion of subject qualification).

Additional bases for exclusion from enrollment were the following:

the leading cause of occlusive arterial disease of the extremities in patients over 40 years old, manifesting as segmental atherosclerotic plaques of usually medium- and large-sized vessels.

²⁰ the inflammatory occlusive disorder of small- and medium-sized arteries and veins in both extremities, most frequently occurring in cigarette-smoking men under age 40 whose ancestors originate in Asia or eastern Europe.

- Females of childbearing potential unless surgically sterilized (bilateral tubal ligation or oophorectomy) or at least 1 year postmenopausal.
- exercise-limiting cardiac disease, including but not limited to:
MI, PTCA, CABG, or hospitalization for angina within 6 months; symptomatic cardiac arrhythmias; exercise-limiting CHF; current exercise-limiting angina pectoris, or angina at rest.
- >200 mmHg supine systolic pressure or >100 mmHg supine diastolic pressure
- Sympathectomy or lower extremity arterial reparative surgery within the previous 3 months.
- Deep vein thrombosis within the past 3 months, excluding isolated calf vein thrombosis.
- history within the previous year of clinically significant bleeding tendencies, hemorrhagic tendencies, or blood dyscrasia, or cerebrovascular hemorrhage, cerebral or dissecting aortic aneurysms, or pericarditis/ pericardial effusions.
- >60% above ideal body weight
- Current malignancy, with the exception of basal cell carcinoma and in situ carcinoma of the cervix
- Active peptic disease.
- Recent or anticipated surgical procedures.
- platelet count below 130,000/cm³ or hematocrit below 30%, twice the upper limit of normal values for AST or ALT, serum creatinine > 2.5 mg/dl
- current alcohol abuse or other drug abuse.
- concurrent use of medications with the following actions: antiplatelet (aspirin, sulfinpyrazone, dipyridamole, ticlopidine) anticoagulant (warfarin, heparin, dicumarol), hemorrheologic (pentoxifylline), or NSAID (with the exception of diclofenac).
- Use of an investigational drug within the past 30 days.

8.3.3 @Qualifying criteria. (study 21-94-201)

After enrollment there was to be at least a 2 week lead-in period during which subjects were to be discontinued from prohibited medications. Subjects then qualified for randomization if the following observations were obtained during standardized treadmill testing conducted prior to study treatment:

- treadmill tests (12.5% incline, speed = 3.2 km/h) terminated for intermittent claudication only.
- ICD 30-200 meters.
- stable ACD \leq 320 meters on a with no greater than 20% variation between the last two visits
- Doppler ABI = 0.90, and at least 10 mmHg decrease in Doppler-measured limb pressure during treadmill testing.

8.3.4 @Treatment regimen. (study 21-94-201)

Qualified subjects were randomized (with stratification by center) to receive placebo, or cilostazol given as a fixed 100 vs 200 mg/d dose in equally-divided twice-daily (b.i.d.) oral administrations for 24 weeks. Cilostazol was packaged as a 50 mg tablet, and a placebo dummy was given to maintain double-blind conditions. Placebo and cilostazol tablets were from lot numbers 4K76PP1 and 4K77PB1, respectively.

8.3.5 @Endpoints. (study 21-94-201)

8.3.5.1 @Endpoint Descriptions (study 21-94-201)

The protocol-specified primary analysis was an assessment of the effects of cilostazol on ICD and ACD at week 24 using analysis of variance of the log of the ratio of the distance at week 24 to the pre-treatment distance, comparing each cilostazol dose to placebo. An amendment prior to the study's initiation (and dated June 23, 1995) made the ACD metric the sole primary endpoint, and relegated ICD to secondary endpoint status. The walking distance endpoints were measured at "trough", i.e. the end of the 12 hour dosing interval.

The prespecified secondary outcome variables were then:

ICD

A composite endpoint including all-cause mortality and cardiovascular morbidity.

This composite endpoint will be discussed in detail in the Safety section of this review ("Pooled Composite Endpoint" subsection). In brief, its components were:

- all-cause mortality
- MI
- Stroke.
- Arterial revascularization.
- Amputation.

- MIs were to be counted, irrespective of whether acute, remote, or silent:

An event was to be classified as acute MI when the subject manifested at least 2 of the following 3 criteria: central chest discomfort for 30 minutes; ≥ 0.1 mv ST segment elevation in at least 2 contiguous leads; total CPK $\geq 150\%$ of the ULN with $\geq 3\%$ MB CPK

An event was to be classified as silent or remote MI when pathologic Q waves were evident in at least 2 contiguous leads. Q waves were to be considered pathologic if they meet the following criteria:

Leads I, II, aVF: .04 seconds in duration, $> .2$ mv amplitude and $> 25\%$ of the amplitude of the succeeding R wave;

Lead aVL: .04 seconds in duration, $> .2$ mv amplitude and $> 15\%$ of succeeding R wave;

Leads V4-V6: .04 seconds in duration, > .2 mv amplitude and > 15% of succeeding R wave;

Lead III: similar to Lead I criteria, but only important if leads II and aVF are also abnormal.

- stroke: defined as any cerebral vascular infarct that causes at least transient symptoms.
- Arterial revascularization: defined as any undertaken on a peripheral, coronary, or carotid artery (including endarterectomy, or stent-placements, with the exception of lower extremity stents).
 - Amputation: for reason other than trauma or tumor.

Other prespecified secondary endpoints were:

- Doppler limb pressures taken at rest, 1 minute, 5 minutes, and 9 minutes post exercise;
- quality of life as assessed by the patient.
- subjective improvement ("therapeutic judgment") as evaluated by the patient vs the physician at the end of the study, relative to pre-treatment, using the following scale: "much better", "better", "unchanged", "worse", "much worse" or "unknown".

In addition, prior to treatment, and again at weeks 2, 4, 8, 12, 16, 20, and 24, measurements of vital signs, hematology, and EKG were obtained (at all but week 16, serum chemistry was also assessed). Urinalysis was performed at weeks 12 and 24; physical examination was performed at week 24.

Doppler-measured limb pressures, and patient-based quality of life questionnaires were assessed at weeks 4, 8, 16, 20, and 24. Blood samples for determination of plasma cilostazol concentrations were obtained at weeks 2, 12 and 24, and forwarded to a central laboratory.

8.3.5.2 @Measurement methods (study 21-94-201)

The "immediate-incline" treadmill method was used wherein the incline load started immediately at 12.5% (and remained constant), with speed also constant at 3.2 km/h (2 mph). Walking tests were administered at weeks 4, 8, 16, 20, and 24, and were only to be stopped for claudication of sufficient severity to cause the subject to be unable to continue walking. There was no prespecified provision for tests to stop for such reasons as reaching an arbitrarily long duration or distance of walking. A calibrated timer and treadmill was used. Attempts were to have been made use the same technician and same treadmill machine in a given patient.